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ORIGINAL ARTICLE

Retrospective Study

Metabolic syndrome does not affect sustained virologic response of direct-acting antivirals while hepatitis C clearance improves hemoglobin A1c

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Abstract

AIM

To determine whether successful treatment with direc-

tacting antivirals (DAA) is associated with improvements in hemoglobin A1c (HbA1c) and if type 2 diabetes mellitus (T2DM) or metabolic syndrome affects sustained virologic response (SVR).

METHODS

We performed a retrospective analysis of all hepatitis C virus (HCV) patients at the VA Greater Los Angeles Healthcare System treated with varying DAA therapy between 2014-2016. Separate multivariable logistic regression was performed to determine predictors of HbA1c decrease $\geqslant$ 0.5 after DAA treatment and predictors of SVR 12-wk post treatment (SVR12).

RESULTS

A total of 1068 patients were treated with DAA therapy between 2014-2016. The presence of T2DM or metabolic syndrome did not adversely affect SVR12. 106 patients had both HCV and T2DM. Within that cohort, patients who achieved SVR12 had lower mean HbA1c pre treatment (7.35 *vs* 8.60, P = 0.02), and lower mean HbA1c post-treatment compared to non-responders (6.55 *vs* 8.61, P = 0.01). The mean reduction in HbA1c after treatment was greater for those who achieved SVR12 than for non-responders (0.79 *vs* 0.01, P = 0.03). In adjusted models, patients that achieved SVR12 were more likely to have a HbA1c decrease of $\geqslant$ 0.5 than those that did not achieve SVR12 (adjusted OR = 7.24, 95%CI: 1.22-42.94).

CONCLUSION

In HCV patients with T2DM, successful treatment with DAA was associated with a significant reduction in HbA1c suggesting that DAA may have a role in improving insulin sensitivity. Furthermore, the presence of T2DM or metabolic syndrome does not adversely affect SVR12 rates in patients treated with DAA.

Key words: Hepatitis C virus; Hemoglobin A1c; Diabetes mellitus; Direct-acting antivirals; Metabolic syndrome

Core tip: The relationship of chronic hepatitis C virus (HCV) and type 2 diabetes mellitus is complex and lesser is known about its relationship to metabolic syndrome. While metabolic syndrome and type 2 diabetes may have had negative outcomes during the era of pegylated-interferon, research is being actively pursued to understand how direct acting antivirals (DAA) may affect these comorbidities. In this study, we show that unlike with pegylated-interferon, direct active antiviral success rates are not affected by the presence of metabolic syndrome. We further show that successful treatment of HCV with DAAs actually leads to better glycemic control 1-year post-treatment.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major worldwide health problem. It is one of the most common blood-borne infections in the United States with an estimated 2.7 million people chronically infected in the United States[1]. HCV is also one of the leading causes of cirrhosis and liver transplantation[1,2]. There are increasing reports indicating an association between HCV and type 2 diabetes mellitus (T2DM). Individuals with HCV are more likely to have risk factors to develop T2DM and patients with T2DM have at least a 2-fold greater risk of developing HCV infection than the general population[3,4].

Prior studies have shown that chronic HCV infection is associated with a greater risk for the development of insulin resistance[5]. In a retrospective analysis of cirrhotic patients, those with HCV infection were 10 times more likely to have T2DM than those without HCV infection[5]. There is evidence that patients with chronic HCV infection and increased insulin resistance have a higher prevalence of hepatic fibrosis, hepatocellular carcinoma, and other extrahepatic manifestations[6-9]. While there are unclear mechanisms for increased insulin resistance among those with HCV, factors such as metabolic syndrome, increased hepatic iron, and serum tumor necrosis factor-α have been implicated[10,11]. Molecular studies have also shown that the mechanism of insulin resistance can differ by HCV genotype. In particular, HCV genotype 3 has been shown to be an independent risk factor for hepatic steatosis and its viral proteins can directly interfere with intracellular insulin signaling[12].

Previously standard therapy for HCV required the use of pegylated interferon-α (P-IFN) and ribavirin. However, these regimens had low sustained virologic response (SVR) rates and were poorly tolerated. During the era of P-IFN therapy, several studies showed that the presence of obesity and/or steatosis led to a reduction of SVR rate in HCV patients[13,14]. In patients with diabetes and HCV who were treated with IFN-based therapies, HCV clearance was associated with improved insulin resistance and beta cell function[15]. In 2013 and 2014, approval of newer direct acting antiviral agents (DAA) created IFN-free regimens with SVR rates greater than 90%, radically changing HCV treatment. Due to the novelty of DAA regimen, research is being actively pursued in a variety of patient populations. Within the Veterans Health Administration (VA), the incidence of chronic HCV is 2-3 times higher than the general public[16]. Additionally, patients that receive care in the

VA also have a higher prevalence of obesity and T2DM compared to the general population[17,18]. Thus, the VA presents an ideal population to evaluate the relationship between HCV and T2DM. We aim to determine if successful treatment with DAA is associated with improvements in hemoglobin A1c (HbA1c) and if the presence of T2DM or metabolic syndrome affects SVR rates.

MATERIALS AND METHODS

Study population and data collection

DAA were introduced to the VA Greater Los Angeles Healthcare System (VAGLAHS) at the beginning of April 2014. Therefore, we included all patients being treated with DAA between April 1st, 2014 and April 30th, 2016 for this study. We queried the Corporate Data Warehouse (CDW), a repository of all clinical data within the VA healthcare system, for all patients with an International Classification of Disease, Ninth Revision and/or Tenth Revision, Clinical Modification (ICD-9 CM/ICD-10 CM) diagnosis of HCV and T2DM (ICD-9: 250.00-250.93, ICD-10: E08-E13). Patients with HCV were also included if they had diabetic medications on their medication list during the study period. Patients were excluded from the cohort if they did not have SVR12 data or HbA1c one year after completion of DAA therapy. In addition to the CDW query, we manually extracted patient clinical and demographic data as well as confirm the diagnosis of T2DM from the VA electronic medical records, the Computerized Patient Record System (CPRS), of all patients screened to have both HCV and T2DM by ICD-9 CM or ICD-10 CM codes.

Outcome variables

The primary outcome was the change in HbA1c before and after DAA treatment. The secondary outcomes of interest were change in body mass index (BMI) over the same time period and if the presence of T2DM or other traits of metabolic syndrome such as hyperlipidemia (HDL), hypertension (HTN), or obesity affected SVR12. Serial BMI and HbA1c values were obtained from the year before and the year after HCV treatment and summarized as one-year pre-treatment and one-year post-treatment averages, respectively. A significant change of HbA1c was defined as a difference of 0.5 or greater, consistent with prior similar studies[19,20]. Through chart review, we also documented whether a patient had an increase or decrease in oral hypoglycemic dose and/or injectable insulin dose from one year before to one year after treatment with DAA. A change of greater than 10% from baseline was considered a significant change in medication, similar to prior studies[21]. Daily insulin was calculated as a total amount of basal and/or meal-time insulin over a 24-h period as documented in the patient's medication list. We also documented if there was a change in the overall number of diabetes medications from one year before to one year after treatment with DAA.

Predictor variables

Data extraction included patient demographic, comorbidity, laboratory, and medication data from CPRS. Demographic data included age, sex, BMI, race, and ethnicity. For race and ethnicity, we used one mutually-exclusive variable that combined concepts of race and ethnicity by including Hispanic as a primary race (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other). Comorbidities included the presence of cirrhosis by chart review, elevated Fibrosis-4 (Fib-4) score (a measure of advanced fibrosis), hyperlipidemia (HLD), hypertension (HTN), HIV, and metabolic syndrome as identified by ICD9/ICD10 codes or by chart review. A cutoff value of 3.25 was used to determine a significant Fib-4 score as consistent with prior studies[22]. Within the cohort of patients with both HCV and T2DM, the presence of cirrhosis, ascites, and hepatic encephalopathy were confirmed by chart review of the patient's hepatology notes. If a patient had cirrhosis, clinical laboratory values were used to calculate a patient's Child-Turcotte-Pugh score and Child-TurcottePugh class (CTP). Using a modified World Health Organization definition for metabolic syndrome, we defined metabolic syndrome as having at least diabetes mellitus and at least two of the following baseline characteristics as determined by ICD-9 CM codes, ICD-10 CM codes, or by medication review: A BMI $\geqslant$ 30 kg/m^2, HTN, and HLD[23]. The presence of HLD was used as a surrogate for elevated triglyceride or reduced HDL cholesterol as we were unable to accurately obtain triglyceride or HDL levels for all patients before statin therapy. Furthermore, because many patients did not have urine albumin or urine creatine measurements, the presence of microalbuminuria was not analyzed. We also documented serological virologic clearance at 12-wk post treatment (SVR12), HCV genotype, and prior HCV treatment for all patients.

Statistical analysis

We performed proportions to summarize demographic and clinical characteristics and used χ^2 tests to examine differences between patients that did achieve SVR12 and those that did not. Medians were compared using the Wilcoxon rank-sum test, and means were compared using analysis of variance (ANOVA). All means are expressed with their respective standard error.

To determine predictors of SVR12, a multivariable logistic regression was performed. Due to the rare event of DAA failure, to examine the relationship between SVR12 and HbA1c, we performed univariable and multivariable penalized maximum likelihood logistic regression analyses similar to prior studies[24,25]. Predictors included age, sex, race/ethnicity, HCV genotype, treatment experienced or naïve, DAA used, and comorbid conditions (HTN, DM, HLD, HIV, elevated Fib-4, obesity, metabolic syndrome). The reference

group was female, white, treatment experienced, low Fib-4, without HTN/HLD/metabolic syndrome, genotype 1a, and treated with sofosbuvir/simeprevir. In addition to this model, we performed sub-analyses to determine associations between SVR12 and change in insulin dose required before and after DAA therapy. Statistical assistance was provided by the Institute for Digital Research and Education at UCLA. This study along with a waiver of informed consent was approved by the VA Institutional Review Board and the Research and Development Committee at VAGLAHS.

RESULTS

Cohort characteristics

A total of 1068 patients met inclusion criteria. Baseline characteristics are summarized in Table 1. In all patients treated with DAA, SVR12 rates differ by age, Fib-4 score, HCV genotype, DAA therapy, and DAA planned duration of treatment. Patients who achieved SVR12 were older (62.0 years *vs* 60.7 years, $P = 0.02$). Patients with a Fib-4 score < 3.25 had an SVR12 rate of 90.9% as compared to 80.2% for patients with a Fib-4 score ⩾ 3.25. SVR12 rates were varied by HCV genotype, with genotype 2 and 3 having lower SVR12 rates than genotype 1 ($P < 0.01$). SVR12 rates also were varied by treatment and duration of therapy. SVR12 rates were highest for patients treated with shorter duration (8 and 12 wk as compared to 16 and 24 wk) and with sofosbuvir/ledipasvir (93.7%) as compared to other regimens.

Of the 1068 patients treated with DAA, 106 patients concomitantly had T2DM and HCV and at least one HbA1c value 1-year post SVR12 (Table 2). The average age was 63.2 years (0.5). Within the cohort, 105 (99.1%) were male, 29 (27.4%) were white, 39 (36.8%) were African-American, and 27 (25.5%) were Hispanic. A total of 98 patients (92.5%) achieved SVR12 and 8 patients (7.5%) did not achieve SVR12. Fifty-seven patients (53.8%) had cirrhosis with a majority (82.5%) being compensated (*i.e.*, CTP A). Seventy-two patients (67.9%) were treatment-naïve while 34 patients (32.1%) had been treated with pegylated-interferon in the past. The majority of patients had genotype 1a ($n = 60$, 56.6%) or 1b ($n = 24$, 22.6%) disease. Only 16 patients (15.1%) had a normal BMI at the time of treatment (⩾ 18 and < 25) while the rest had a BMI ⩾ 25. Only 3 patients (2.8%) were co-infected with HIV. Ninety-five patients (89.6%) had HTN, 79 (74.5%) had HLD, and 85 (80.2%) had metabolic syndrome.

The average age for patients who achieved SVR12 was higher than those who did not (63.5 years *vs* 59.6 years, respectively, $P = 0.04$). There were no significant differences between patients who achieved SVR12 and those who did not in regards to sex, race/ethnicity, presence of cirrhosis, prior treatment experience, HCV genotype, treatment regimen, BMI, HIV status, HTN, HLD, or metabolic syndrome (Table 2).

Changes in HbA1c and BMI

Overall, average HbA1c was significantly lower after DAA therapy: 7.44% *vs* 6.71%, $P = 0.01$. For the subgroup of patients that achieved SVR12, the average HbA1c before treatment was significantly higher than the average after treatment (7.35% *vs* 6.55%, $P < 0.01$). When SVR12 was not achieved, however, HbA1c was not significantly different before and after treatment: 8.60% *vs* 8.61%, $P = 0.99$ (Table 3). This relationship was preserved across all genotypes with the greatest difference occurring in genotype 3 (Table 3). However, there was no difference in the change of HbA1c between genotypes or treatment regimens (Table 4).

Forty-six patients were on insulin before treatment and 43 patients were on insulin after treatment. Of those patients who were on insulin, the average daily insulin requirement before treatment was 55.1 IU (5.7) and 49.7 IU (6.2) after treatment ($P = 0.50$). For patients on insulin who achieved SVR12, the average daily insulin requirement before treatment was 55.0 IU (5.85) and the average daily insulin requirement after treatment was 48.2 IU (6.30) ($P = 0.42$). Insulin requirement also did not change significantly for patients who did not achieve SVR12 [55.5 IU (20.4) *vs* 58.1 IU (21.8), $P = 0.93$]. No patients analyzed were on any non-insulin injectable diabetes medications. There was no difference between the number of diabetes medications per patient before or after DAA therapy (1.23 *vs* 1.26, $P = 0.43$).

The study included 44 patients (41.5%) defined as overweight (BMI ⩾ 25), 30 (28.3%) that were defined as obese (BMI ⩾ 30), and 12 (10.4%) with severe obesity (BMI ⩾ 40). The average BMI for all patients before treatment was 30.1 kg/m^2 (0.53), and the average BMI for all patients after treatment was 30.2 kg/m^2 (0.54) ($P = 0.92$). For patients who achieved SVR12, the average BMI before and after treatment were not statistically different: 30.3 kg/m^2 (0.56) *vs* 30.3 kg/m^2 (0.57), $P = 0.96$. Similarly, the average BMI was not different before and after treatment for the patients that did not achieve SVR12: 28.8 kg/m^2 (1.4) *vs* 29.2 kg/m^2 (1.5), $P = 0.92$.

SVR12 is not affected by the components of metabolic syndrome

After adjusting for age, sex, race/ethnicity, cirrhosis, treatment experience, HCV genotype, treatment regimen, HIV status, and treatment duration, the individual components of metabolic syndrome (obesity, HTN, HLD, and T2DM) and the presence of metabolic syndrome itself did not predict SVR12 (Table 5). For the full logistic regression for SVR12, please see supplemental Table 1.

SVR12 as a predictor of improved insulin resistance

When adjusting for age, sex, race/ethnicity, cirrhosis,

Table 1 Baseline characteristics of all patients treated with direct-acting antivirals *n* (%)

	All patients (*n* = 1068)	SVR12 not achieved (*n* = 138)	SVR12 achieved (*n* = 930)	*P*-value
Age (mean ± SE, yr)	61.8 ± 0.2	60.7 ± 0.5	62.0 ± 0.2	0.02
Sex				
Male	97.5 (1041)	12.8 (133)	87.2 (908)	0.78
Female	2.5 (27)	18.500 (5)	81.50 (22)	
Race/ethnicity				
White	37.5 (400)	11.00 (44)	89.0 (356)	0.14
African American	37.5 (401)	14.70 (59)	85.3 (342)	
Hispanic	15.1 (161)	16.80 (27)	83.2 (134)	
Asian	0.70 (7)	14.30 (1)	85.700 (6)	
Other	9.3 (99)	7.10 (7)	92.90 (92)	
Fib4 < 3.25	64.6 (690)	9.1 (63)	90.9 (627)	< 0.01
Fib4 ⩾ 3.25	35.4 (378)	19.80 (75)	80.2 (303)	
Treatment naïve	79.5 (849)	16.4 (102)	83.6 (747)	0.09
Treatment experienced	20.5 (219)	16.40 (36)	83.6 (183)	
HCV genotype				
HCV genotype 1a	58.0 (619)	12.10 (75)	87.9 (544)	< 0.01
HCV genotype 1b	25.9 (277)	10.10 (28)	89.9 (249)	
HCV genotype 2	7.9 (84)	21.40 (18)	78.60 (66)	
HCV genotype 3	6.9 (74)	23.00 (17)	77.00 (57)	
HCV genotype 4	1.2 (13)	0.00 (0)	100.0 (13)	
HCV genotype 6	0.10 (1)	0.00 (0)	100.0 (1)	
Treatment				
PrOD	4.5 (48)	8.30 (4)	91.70 (44)	0.01
PrOD/RBV	17.6 (188)	14.40 (27)	85.6 (161)	
Sofosbuvir/Ledipasvir	34.4 (367)	6.3 (23)	93.7 (344)	
Sofosbuvir/Ledipasvir/RBV	13.4 (143)	13.30 (19)	86.7 (124)	
Sofosbuvir/RBV	9.8 (105)	23.80 (25)	76.20 (80)	
Sofosbuvir/Simeprevir	17.5 (187)	19.80 (37)	80.2 (150)	
Other regimens	2.9 (30)	10.0 (3)	90.00 (27)	
No HIV	96.7 (1033)	13.1 (135)	86.9 (898)	0.44
HIV	3.3 (35)	8.60 (3)	91.40 (32)	
Duration of treatment				
8 wk	19.9 (213)	6.6 (14)	93.4 (199)	< 0.01
12 wk	73.1 (781)	13.4 (105)	86.6 (676)	
16 wk	2.8 (30)	40.00 (12)	60.00 (18)	
24 wk	4.1 (44)	15.90 (7)	84.10 (37)	
BMI < 30	66.5 (710)	12.50 (89)	87.5 (621)	0.60
BMI > 30	33.5 (358)	13.70 (49)	86.3 (309)	
No HTN	43.7 (467)	13.30 (62)	86.7 (405)	0.76
HTN	56.3 (601)	12.60 (76)	87.5 (525)	
No T2DM	85.6 (914)	12.4 (113)	87.6 (801)	0.15
T2DM	14.4 (154)	16.20 (25)	83.8 (129)	
No HLD	58.1 (620)	14.50 (90)	85.5 (530)	0.70
HLD	41.9 (448)	10.70 (48)	89.3 (400)	
No metabolic syndrome	87.1 (930)	13.0 (121)	87.0 (809)	0.84
Metabolic syndrome	12.9 (138)	12.30 (17)	87.7 (121)	

PrODL: Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir; Fib4: Fibrosis 4 score; RBV: Ribavirin; BMI: Body mass index; HTN: Hypertension; T2DM: Type 2 diabetes mellitus; HLD: Hyperlipidemia; SVR: Sustained virologic response; HCV: Hepatitis C virus.

treatment experience, HCV genotype, treatment regimen, obesity, HIV status, HTN, HLD, and metabolic syndrome, SVR12 significantly predicted a 0.5-unit improvement in HbA1c with treatment in patients with both T2DM and HCV: Adjusted OR (aOR) = 7.24 (95%CI: 1.22-42.94) (Table 6). Patients who achieved SVR12 were also significantly less likely to require an increase in insulin after HCV therapy than those who did not achieve SVR12: aOR = 0.166 (95%CI: 0.03-0.74). A decrease of HbA1c was not associated with an increase in oral hypoglycemic dose (aOR = 1.07, 95%CI: 0.48-1.35) or injectable insulin dose (aOR = 0.6, 95%CI: 0.57-1.87) after DAA therapy.

DISCUSSION

This study demonstrates that HCV clearance with DAAs is associated with a clinically significant decrease in HbA1c independent of other demographic and clinical factors such as metabolic syndrome and BMI. This data corroborates recent studies that showed similar outcomes with DAA therapy[26]. While Hum *et al*[26] attempted to control for DM medication use by looking at the percent of patients taking any DM medication or by the number of DM medication class, being unable to look at dosage change or changes in medication for an individual patient was a limitation of their study.

Table 2 Baseline characteristics of patients with hepatitis C virus and type 2 diabetes mellitus

	All patients (n = 106)	SVR12 not achieved (n = 8)	SVR12 achieved (n = 98)	P-value
Age (mean ± SD, yr)	63.2 ± 0.5	59.6 ± 1.4	63.5 ± 0.5	0.04
Sex				
Male	99.1 (105)	7.60 (8)	92.40 (97)	0.74
Female	0.90 (1)	0.00 (0)	100.0 (1)	
Race/ethnicity				
White	27.40 (29)	6.90 (2)	93.20 (27)	0.15
African American	36.80 (39)	5.10 (2)	94.90 (37)	
Hispanic	25.50 (27)	11.1 (3)	88.90 (24)	
Asian	1.90 (2)	50.0 (1)	50.00 (1)	
Other	8.50 (9)	0.00 (0)	100.0 (9)	
Cirrhosis				
Yes	53.80 (57)	8.80 (5)	91.20 (52)	0.61
No	46.20 (49)	6.10 (3)	93.90 (46)	
CTP class				
CTP A	82.50 (47)	6.40 (3)	93.60 (44)	0.21
CTP B	14.00 (8)	25.0 (2)	75.0 (6)	
CTP C	3.50 (2)	0.00 (0)	100.0 (2)	
Treatment status				
Naive	67.90 (72)	5.60 (4)	94.40 (68)	0.26
Experienced	32.10 (34)	11.8 (4)	88.20 (30)	
HCV genotype				
Genotype 1a	56.60 (60)	10.0 (6)	90.00 (54)	0.67
Genotype 1b	22.60 (24)	4.20 (1)	95.80 (23)	
Genotype 2	12.30 (13)	0.00 (0)	100.0 (13)	
Genotype 3	7.60 (8)	12.5 (1)	87.50 (7)	
Genotype 4	0.90 (1)	0.00 (0)	100.0 (1)	
Treatment regimen				
Sofosbuvir/Simeprevir	39.60 (42)	7.10 (3)	92.90 (39)	0.96
Sofosbuvir/Ribavirin	17.00 (18)	5.60 (1)	94.40 (17)	
PrOD	18.90 (20)	10.0 (2)	90.00 (18)	
Sofosbuvir/Ledipasvir	24.50 (26)	7.70 (2)	92.30 (24)	
Body mass index				
Normal	15.10 (16)	6.20 (1)	93.80 (15)	0.78
Overweight	41.50 (44)	9.10 (4)	90.90 (40)	
Obese	28.30 (30)	6.70 (2)	93.30 (28)	
Severely obese	10.40 (12)	8.30 (1)	91.70 (11)	
Very severely obese	4.70 (4)	0.00 (0)	100.0 (4)	
Co-HIV infection	2.80 (3)	100.0 (3)	0.0 (0)	0.62
HTN	89.60 (95)	8.40 (8)	91.60 (87)	0.32
HLD	74.50 (79)	6.30 (5)	93.70 (74)	0.42
Metabolic syndrome	80.20 (85)	7.10 (6)	92.90 (79)	0.71

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HTN: Hypertension; HLD: Hyperlipidemia; PrOD: Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir; SVR: Sustained virologic response; CTP: Child-Turcotte-Pugh.

By analyzing each individual patient and examining both changes in the number of DM medication and the dosage, we find that the change of HbA1c was not due to an increase in oral hypoglycemic or insulin treatment. The findings imply that the change in HbA1c was most likely due to a change in host insulin resistance due to HCV clearance. This is in line with a recent study showing that HCV clearance with DAA reverses insulin resistance[27]. Our finding, however, is contrary to what Chaudhury *et al*[28] described in their recent paper published in December of 2017. While their study showed no change in HbA1c with DAA therapy, only 17% of patients had diabetes and their average baseline HbA1c was 5.75%. A reduction in HbA1c in a non-diabetic patient is hard to achieve. Therefore, it is reasonable to suggest that if they only examined patients with T2DM with a baseline HbA1c $\geqslant$ 6.5% they would have found similar conclusions. Our data is further corroborated by data showing that successful treatment with DAA is also associated with a decreased likelihood of requiring higher insulin doses for DM management. This is contrary to a paper by Stine *et al*[29] showing that a third of patients required an increase in their DM medication after DAA therapy. However, they only examined patients up to the time of SVR12. It is possible that if they examined data one year after SVR12 they would have had similar results. Our study also shows that changes in HbA1c did not vary between HCV genotype and DAA treatment regimen, implying that HCV clearance itself plays an important role in insulin resistance. Even though the baseline HbA1c was different in those who did achieve SVR12 compared to those that did not, our study shows that metabolic syndrome or its individual components

Table 3 Mean hemoglobin A1c before and after hepatitis C virus treatment by hepatitis C virus genotype and sustained virologic response 12-wk status

Genotype	Before DAA	SE	After DAA	SE	*P*-value
Mean HbA1c of patients who did achieve SVR12					
1a	7.5	0.19	6.68	0.14	0.001
1b	7.3	0.22	6.59	0.21	0.03
2	7.09	0.35	6.29	0.21	0.06
3	7.12	0.37	6.10	0.39	0.08
4	5.5	NA	5.30	NA	NA
Overall	7.35	0.13	6.55	0.11	< 0.01
Mean HbA1c of patients who did not achieve SVR12					
1a	8.98	1.14	8.95	1.41	0.98
1b	6.4	NA	6.50	NA	NA
2	No observations				
3	8.5	NA	8.70	NA	NA
4	No observations				
Overall	8.6	0.89	8.61	1.08	0.99

HbA1c: Hemoglobin A1c; SVR12: Sustained virologic response 12 wk after treatment; DAA: Direct acting antiviral; SE: Standard error.

Table 4 Mean difference in hemoglobin A1c by hepatitis C virus genotype and direct acting antiviral treatment

	Average change HbA1c (SE)	*P*-value
HCV genotype		
1a	-0.73 (0.13)	0.97
1b	-0.69 (0.20)	
2	-0.79 (0.27)	
3	-0.88 (0.51)	
4	-0.20 (NA)	
Treatment		
Sofosbuvir/Simeprevir	-0.71 (0.16)	0.97
Sofosbuvir/Ribavirin	-0.77 (0.27)	
PrOD	-0.66 (0.15)	
Ledipasvir/Sofosbuvir	-0.80 (0.24)	

HbA1c: Hemoglobin A1c; HCV: Hepatitis C virus; PrOD: Ombitasvir/ Paritaprevir/Ritonavir/ Dasabuvir

Table 5 Components of metabolic syndrome on Sustained virologic response 12 wk after treatment

	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Obese	0.90 (0.62-1.31)	1.25 (0.82-1.90)
HTN	1.06 (0.74-1.52)	0.81 (0.51-1.28)
HLD	1.42 (0.97-2.10)	1.31 (0.87-1.97)
T2DM	0.72 (0.48-1.10)	0.82 (0.55-1.09)
Metabolic syndrome	1.04 (0.68-1.60)	1.81 (0.75-4.37)

HTN: Hypertension; HLD: Hyperlipidemia; T2DM: Type 2 diabetes mellitus.

(HTN, T2DM, Obesity, HLD) does not negatively affect SVR12 rates.

Prior studies have demonstrated an association between HCV infection and host metabolism. It has been shown that the hepatitis C virus depends on host lipids for entry and replication in hepatocytes[30-32]. HCV infection, in return, leads to a disruption of host metabolism, which can result in insulin resistance, lipid dysregulation, and hepatic steatosis[33].

The data represented here are consistent with data during the pegylated-interferon era where SVR clearance was associated with decreased insulin resistance and improved beta-cell function[10,15,34,35]. Kawaguchi *et al*[15], for example, demonstrated a three-fold increase in insulin receptor substrate 1 and 2 expressed in hepatocytes in 29 biopsy-proven HCV infection who maintained SVR after pegylated-interferon therapy. They also demonstrated a correlation between serum ferritin and homeostatic model assessment (HOMA) of β-cell function. Their data supports prior data that shows hepatic iron-induced oxidative stress may be related to insulin resistance[36]. Knobler *et al*[11] proposed an alternative mechanism in which HCV infection may mediate diabetes. In a comparison of 23 patients with DM and HCV to 28 patients with HCV alone, they showed that serum TNF-α levels were more prominent in those with concurrent DM. This is similar to prior data that shows that TNF-α signaling may be related to obesity and insulin resistance, thus suggesting a role of inflammation in creating a "diabetogenic" state[37].

During the era of pegylated-interferon, Bressler *et al*[14] showed that obesity was an independent risk factor for reduced SVR12. Because pegylated-interferon is primarily taken up in the lymphatic system and because obese patients have poor lymphatic circulation, they proposed that the difference they described was due to dissimilar pharmacokinetic properties of obese and non-obese patients. While that may have been true for pegylated-interferon, our study shows that obesity, HTN, T2DM, or HLD does not significantly affect SVR12 rates of patients on DAA therapy. Unsurprisingly, SVR12 rates were reduced in patients with an elevated Fib-4 score, in patients with genotype 3, and in patients treated with suboptimal regimens such as sofosbuvir/ribavirin or sofosbuvir/simeprevir. This is similar to prior studies showing reduced SVR12 in similar treated groups[38-40]. We further hypothesized that patients who were more ill were more likely to be treated for a longer duration thus explaining the discrepancy between SVR rates and treatment duration.

While this study demonstrates the interplay between host metabolisms with HCV infection, there are certain limitations. The study implies that HCV clearance is associated with a reduction in insulin resistance, however, we were unable to measure insulin resistance directly before and after treatment. With primary care providers preferentially using HbA1c over fasting blood glucose, we were unable to use HOMA-IR (insulin resistance), HOMA-β (β-cell function), or other indices of insulin resistance. Nonetheless, HbA1c is a well-accepted and commonly utilized method to evaluate for insulin sensitivity, and we feel that using HbA1c as an outcome is consistent with clinical diagnosis, management, and prior studies[18,20]. Second,

Table 6 Odds ratio for a decrease of hemoglobin A1c > 0.5 among type 2 diabetes mellitus patients treated with direct acting antiviral

Predictor	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Age	1.03 (0.95-1.11)	1.07 (0.96-1.20)
Race/ethnicity		
White[1]	1.58 (0.64-3.91)	
African American	0.89 (0.32-2.43)	0.52 (0.13-2.06)
Hispanic	0.53 (0.18-1.57)	0.65 (0.16-2.66)
Asian	0.50 (0.02-8.85)	0.8 (0.04-10.01)
Other	0.83 (0.16-4.21)	0.98 (0.12-7.90)
Cirrhosis (by chart review)	0.62 (0.28-1.37)	0.59 (0.20-1.69)
Treatment naïve	0.84 (0.87-4.59)	2.61 (0.92-7.29)
HCV genotype		
1a[1]	0.77 (0.35-1.71)	
1b	1.33 (0.49-3.60)	0.79 (0.22-2.86)
2	1.50 (0.41-5.42)	6.75 (0.26-176.51)
3	0.66 (0.15-2.92)	3.81 (0.29-50.00)
Treatment regimen		
Sofosbuvir/Simeprevir[1]	1.23 (0.55-2.75)	
Sofosbuvir/Ribavirin	0.75 (0.27-2.09)	0.07 (0.003-1.50)
PrOD	1.60 (0.56-4.56)	0.71 (0.17-2.86)
Ledipasvir/Sofosbuvir	0.66 (0.27-1.62)	0.35 (0.09-1.36)
Overweight	1.36 (0.42-4.35)	0.89 (0.20-1.69)
Obese	1.55 (0.44-5.40)	1.10 (0.20-5.93)
Severely obese	1.08 (0.24-4.94)	0.41 (0.05-3.07)
Very severely obese	0.26 (0.21-3.06)	0.08 (0.003-2.07)
HTN	1.36 (0.38-4.80)	1.15 (0.15-8.86)
HLD	1.69 (0.69-4.09)	1.45 (0.29-7.26)
Metabolic syndrome	1.58 (0.60-4.15)	0.96 (0.10-9.19)
SVR12[a]	10.67 (1.76-64.7)	7.24 (1.22-42.94)

[1]Reference group; [a]$P < 0.05$. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HTN: Hypertension; HLD: Hyperlipidemia; SVR12: Sustained virologic response 12 wk post-treatment; PrOD: Ombitasvir/Paritaprevir/Ritonavir/ Dasabuvir.

our study was a single center study conducted in the VA. VA patients are predominantly male and have different socioeconomic factors that may affect health as compared to the general population. Nonetheless, GLAVA is one of the largest VA medical center that includes an integrated network of 12 sites serving a racially and ethnically diverse population in Southern California.

In conclusion, this study of a diverse VA patient population demonstrates that HCV clearance with DAAs is associated with a clinically significant decrease in HbA1c. This change was consistent across all genotypes and treatment regimens. The change in HbA1c was independent of changes in BMI and DM medication requirements and so may represent a decrease in host insulin resistance or increased insulin sensitivity. This study substantiates similar studies during the pegylated-interferon era by showing that HCV clearance irrespective of treatment regimen and genotype leads to improved DM outcomes. However, unlike prior studies during the period of pegylated-interferon, we show that HTN, HLD, T2DM, obesity, and metabolic syndrome do not negatively affect SVR12 rates for DAA. Future prospective studies analyzing patient fasting blood glucose and serum insulin should be performed to validate these findings and to help elucidate the relationship between HCV, insulin sensitivity, and longer-term DM outcomes such as cardiovascular events.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV) infection is a major worldwide health problem. There are increasing reports indicating an association between HCV and type 2 diabetes mellitus (T2DM). Individuals with HCV are more likely to have risk factors to develop T2DM and patients with T2DM have at least a 2-fold greater risk of developing HCV infection than the general population. Previously standard therapy for HCV required the use of pegylated interferon-α (P-IFN) and ribavirin. However, these regimens had low sustained virologic response (SVR) rates and were poorly tolerated. During the era of P-IFN therapy, several studies showed that the presence of obesity and/or steatosis led to a reduction of SVR rate in HCV patients. In patients with diabetes and HCV who were treated with IFN-based therapies, HCV clearance was associated with improved insulin resistance and beta cell function.

Research motivation

In 2013 and 2014, approval of newer direct acting antiviral agents (DAA) created IFN-free regimens with SVR rates greater than 90%, radically changing HCV treatment. Due to the novelty of DAA regimen, research is being actively pursued in a variety of patient populations.

Research ojectives

We aim to determine if successful treatment with DAA is associated with improvements in hemoglobin A1c (HbA1c) and if the presence of T2DM or metabolic syndrome affects SVR rates.

Research methods

DAA were introduced to the VA Greater Los Angeles Healthcare System (VAGLAHS) at the beginning of April 2014. Therefore, we included all patients being treated with DAA between April 1st, 2014 and April 30th, 2016 for this study.

We performed a retrospective analysis of all HCV patients at the VA Greater Los Angeles Healthcare System treated with DAA therapy between 2014-2016. Separate multivariable logistic regression was performed to determine predictors of HbA1c decrease $\geqslant$ 0.5 after DAA treatment and predictors of SVR 12-wk post treatment (SVR12). Patients with HCV were also included if they had diabetic medications on their medication list during the study period. Patients were excluded from the cohort if they did not have SVR12 data or a HbA1c one year after completion of DAA therapy.

Research results

A total of 1068 patients were treated with DAA therapy between 2014-2016. The presence of T2DM or metabolic syndrome did not adversely affect SVR12. 106 patients had both HCV and T2DM. Within that cohort, patients who achieved SVR12 had lower mean HbA1c pre-treatment (7.35 *vs* 8.60, P = 0.02), and lower mean HbA1c post-treatment compared to non-responders (6.55 *vs* 8.61, P = 0.01). The mean reduction in HbA1c after treatment was greater for those who achieved SVR12 than for non-responders (0.79 *vs* 0.01, P = 0.03). In adjusted models, patients that achieved SVR12 were more likely to have a HbA1c decrease of > 0.5 than those that did not achieve SVR12 (adjusted OR = 7.24, 95%CI: 1.22-42.94).

Research conclusions

In conclusion, this study of a diverse VA patient population demonstrates that HCV clearance with DAAs is associated with a clinically significant decrease in HbA1c. This change was consistent across all genotypes and treatment regimens. The change in HbA1c was independent of changes in BMI and DM medication requirements and so may represent a decrease in host insulin resistance or increased insulin sensitivity. This study substantiates similar studies during the pegylated-interferon era by showing that HCV clearance irrespective of treatment regimen and genotype leads to improved DM outcomes. However, unlike prior studies during the period of pegylated-interferon, we show that hypertension, hyperlipidemia, T2DM, obesity, and metabolic syndrome do not negatively affect SVR12 rates for DAA.

Research perspectives

Future prospective studies analyzing patient fasting blood glucose and serum insulin should be performed to validate these findings and to help elucidate the relationship between HCV, insulin sensitivity, and longer-term DM outcomes such as cardiovascular events.

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